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Original Article

Pilot multi-centre randomised trial of the impact of pre-operative focused cardiac ultrasound on mortality and morbidity in patients having surgery for femoral neck fractures (ECHONOF-2 pilot)

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Summary

Hip fracture surgery is common, usually occurs in elderly patients who have multiple comorbidities, and is associated with high morbidity and mortality. Pre-operative focused cardiac ultrasound can alter diagnosis and management, but its impact on outcome remains uncertain. This pilot study assessed feasibility and group separation for a proposed large randomised clinical trial of the impact of pre-operative focused cardiac ultrasound on patient outcome after hip fracture surgery. Adult patients requiring hip fracture surgery in four teaching hospitals in Australia were randomly allocated to receive focused cardiac ultrasound before surgery or not. The primary composite outcome was any death, acute kidney injury, non-fatal myocardial infarction, cerebrovascular accident, pulmonary embolism or cardiopulmonary arrest within 30 days of surgery. Of the 175 patients screened, 100 were included as trial

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participants (screening:recruitment ratio 1.7:1), 49 in the ultrasound group and 51 as controls. There was one protocol failure among those recruited. The primary composite outcome occurred in seven of the ultrasound group patients and 12 of the control group patients (relative group separation 39%). Death, acute kidney injury and cerebrovascular accident were recorded, but no cases of myocardial infarction, pulmonary embolism or cardiopulmonary arrest ocurred. Focused cardiac ultrasound altered the management of 17 participants, suggesting an effect mechanism. This pilot study demonstrated that enrolment and the protocol are feasible, that the primary composite outcome is appropriate, and that there is a treatment effect favouring focused cardiac ultrasound – and therefore supports a large randomised clinical trial.

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Introduction

Hip fracture patients are typically elderly and suffer from multiple comorbid diseases. Despite advances in healthcare, both 30-day and 1-year postoperative mortality remain high at 7.1% (England and Wales) [1] and 20–35% (Europe) [2], respectively. Death most commonly results from comorbidities rather than the hip fracture. Postoperative morbidity is common, often disabling, and can require prolonged, expensive institutionalisation. Prolonged longevity suggests that the annual incidence of hip fracture worldwide could rise from 2.3 million currently to 6.3 million by 2050 [3].

Adequate pre-operative assessment is prudent in patients who are at high risk of cardiac disease [4]. However, there is also evidence that delaying surgery increases postoperative mortality [5–7], constraining the time available for pre-operative investigations. Clinical assessment of cardiac disease is unreliable, misdiagnosing significant cardiovascular disease in about half of all patients [8–10]. Transthoracic echocardiography is a non-invasive investigation that identifies structural cardiac pathologies independently associated with postoperative mortality, such as cardiac failure [11], aortic stenosis [12] and pulmonary hypertension [13]. Transthoracic echocardiography also identifies abnormal haemodynamic states, including hypovolaemia, cardiac failure and vasodilation [14], allowing rapid correction of these before anaesthesia and surgery.

However, formal echocardiographic evaluation by cardiologists may not be routinely available in the short period required available before timely surgery [15]. Focused cardiac ultrasound is a goal-directed, abbreviated form of echocardiography, which enhances bed-side clinical assessment and guides acute medical decisions [16]. Without delaying surgery, focused cardiac ultrasound promotes diagnostic accuracy, often changing diagnosis and management [8, 17], for example, by guiding pre-operative intravascular volume replacement, and rationalising the use of invasive monitoring, vasopressor infusions and planned postoperative intensive care.

In a two-centre retrospective cohort analysis of hip fracture patients, the use of ultrasound was associated with a three-fold reduction in 30-day mortality, compared with a control group with similar risk factors [8]. This pilot study aims to inform the feasibility of conducting a larger multi-centre, prospective randomised controlled trial, to test the hypothesis that compared with controls, focused cardiac ultrasound alters the medical management of hip fracture patients and reduces a collapsed composite of serious complications and mortality 30 days after surgery.

Methods

This parallel group, randomised, controlled, multicentre pilot study with 1:1 allocation ratio was approved by the Melbourne Health Research Ethics Committee. Written consent was obtained from all participants or next of kin with power of attorney.

The main research site was a metropolitan tertiary university hospital with a high volume of acute orthopaedic

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surgery and sufficient clinicians proficient in focused cardiac ultrasound. Three similar centres participated in recruitment at varying times during the study period. The trial did not have per-participant funding which reduced the potential recruitment to days when researchers were available, and for some institutions, a limited duration of recruitment.

Adult participants were eligible for inclusion if they were scheduled for surgical repair of unilateral fractured neck of femur (fracture between the femoral head and a line 5 cm below the lesser trochanter). Participants were not studied if they had received previous hip surgery on the affected side, were scheduled to receive surgery for other injuries, had metastatic cancer or a suspected pathological hip fracture, were not expected to survive longer than 24 h, had undergone echocardiography within one month of the current surgery or had received a request for echocardiography before recruitment and random allocation in the study.

Research personnel monitored the emergency surgery operating theatre list for patients scheduled for hip fracture surgery. Potential participants were then screened for eligibility by review of their medical notes and bed-side assessment. After written informed consent, eligible participants were randomly allocated to either receive pre-operative focused cardiac ultrasound (ultrasound group) or not to receive pre-operative focused cardiac ultrasound (control group). The screening researcher opened a sealed opaque envelope to reveal the group allocation, which was produced by computer-generated random number software (https://www.randomizer.org/) arranged by a non-investigator and hidden from research personnel until outcome data was obtained.

Participants in the ultrasound group received focused cardiac ultrasound within 24 h of planned surgery. The written ultrasound report (Appendix S1) was placed in a sealed envelope. At the time of surgery, the anaesthetist completed a diagnosis and management plan on a research form after their standard clinical assessment, which included their usual patient history and physical examination and review of the medical record and results of investigations. The anaesthetist then reviewed the concealed ultrasound report, before repeating their diagnosis and management plan. This allowed the research team to determine the influence, if any, on diagnosis and management influenced by the ultrasound findings. The ultrasound report was replaced in the opaque envelope and sealed, to blind researchers to the findings of the ultrasound. This is partial blinding as the peri-operative staff could pass on the ultrasound information to other members of the treating team and the group allocation was not concealed from the research nurses who performed patient recruitment, randomisation and outcome data collection.

Participants in the control group did not receive ultrasound but the anaesthetist was still requested to complete the same diagnosis and management forms. Control group participants were not prohibited by the study protocol from having additional investigations after randomisation, including conventional echocardiography.

Focused cardiac ultrasound was performed by trained clinicians according to the iHeartScan™ protocol (haemodynamic echocardiography assessment in real time, Ultrasound Education Group, Department of Surgery, University of Melbourne, VIC, Australia) [18], and who fulfilled the criteria for training in goal-focused cardiac ultrasound from the Australian and New Zealand College of Anaesthetists professional recommendations [19]. This protocol uses pattern recognition of two-dimensional and colour flow Doppler images, to identify clinically important cardiac pathology, defined as: either left ventricular (LV) systolic or diastolic dysfunction, right ventricular (RV) systolic dysfunction, moderate or severe valve stenosis or regurgitation [20, 21], or pericardial effusion of greater than 0.5 cm. Left ventricular systolic dysfunction was defined as systolic fractional reduction in LV internal dimension less than 24% or a reduction in LV end diastolic area less than 50%. Left ventricular diastolic dysfunction was defined as normal LV systolic function with raised left atrial pressure determined by the presence of a fixed curvature of the interatrial septum towards the right atrium, as demonstrated by Haji et al. [22]. Right ventricular dysfunction was defined using ultrasound as dilation of the RV end-diastolic area to greater than two-thirds of the LV end-diastolic area and reduced RV free wall motion with or without flattening of the interventricular septum. The haemodynamic state was assessed

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with ultrasound by categorisation into normal, empty, vasodilated, LV systolic and/or diastolic failure, or RV failure, as described previously [14] using the assessment of LV and RV volume and contractility, and movement and position of the interatrial septum. Clinically insignificant findings included mild valvular stenosis or regurgitation, or mild reduction in systolic ventricular function.

There were no guidelines or restrictions on the peri-operative management of participants in the study by anaesthetists.

In all four participating hospitals, surgery is typically undertaken within 48 h of hospital admission after hip fracture. Participants in both groups received review and management by internal medicine or orthogeriatricians as early as practicable during their hospital stay.

The feasibility outcomes of this one-year pilot study were: to achieve a screening: recruitment ratio below 4:1; to quantify the protocol failure rate; to recruit at least one participant per site per week; to achieve group separation for the primary outcome of $\geq$ 20%; to determine whether ultrasound delayed surgery; to assess barriers to recruitment/site activation; to achieve $\geq$ 25% change in cardiac diagnosis and clinical management in participants undergoing ultrasound compared with controls; and to determine a sample size in the main study based on primary outcome effect size, recruitment ratio and protocol failure rates.

The primary outcome of the proposed trial is a 30-day postoperative composite outcome of all-cause death, acute kidney injury [23] and cardiovascular morbidity (non-fatal myocardial infarction, stroke, pulmonary embolism or cardiac arrest [24]). Definitions of component outcomes are from the European Society of Anaesthesiologist's and Intensive Care Medicine joint taskforce on peri-operative outcome measures [25] and are shown in Appendix S2. Research nurses obtained the morbidity and mortality data from the hospital records, general practitioner and the medical residential facility where required. The cause of death was obtained from the death certificates. These outcomes were assessed by the principal researcher from the data collected by the research nurses, and by review of discharge summaries or case notes as required. A second clinician blinded to allocation performed primary outcome data verification; if there was disagreement, a third blinded reviewer would adjudicate outcome. In the definitive pragmatic trial there will be an independent data monitoring team of clinicians to adjudicate morbid endpoints. The pre-operative comorbidities were obtained from the medical record (including the pre-operative assessment from the treating anaesthetist) and recorded by the research nurses.

The secondary outcomes of the proposed trial are shown in Appendix S2.

Results

Recruitment occurred between 1 February and 26 December 2016 at the primary study site, with four other sites activated during this time-period. One site did not recruit participants, as activation occurred just before conclusion of recruitment for the pilot study (Table 1). The mean (SD) screening: recruitment ratio was 1.7 (0.2), and all sites recruited at least one participant per week. There was one protocol violation where a participant randomly allocated to the ultrasound group did not receive ultrasound before surgery due to unavailability of suitable personnel; the participant remained in the ultrasound group on an intention-to-treat basis. After random allocation, two participants were not studied as the participants were subsequently

Table 1 Site recruitment.

Site	Study duration; weeks	Screened; n	Screened; n.week^{-1}	Recruited; n	Recruited; n.week^{-1}	Screening: recruitment ratio
Royal Melbourne	47	110	2.3	59	1.3	1.9:1
Western General	18	37	2.1	23	1.3	1.6:1
Prince Charles	6	21	3.5	15	2.5	1.4:1
Queen Elizabeth	2	7	3.5	5	2.5	1.4:1
Total	47	175	3.7	102	2.2	1.7:1

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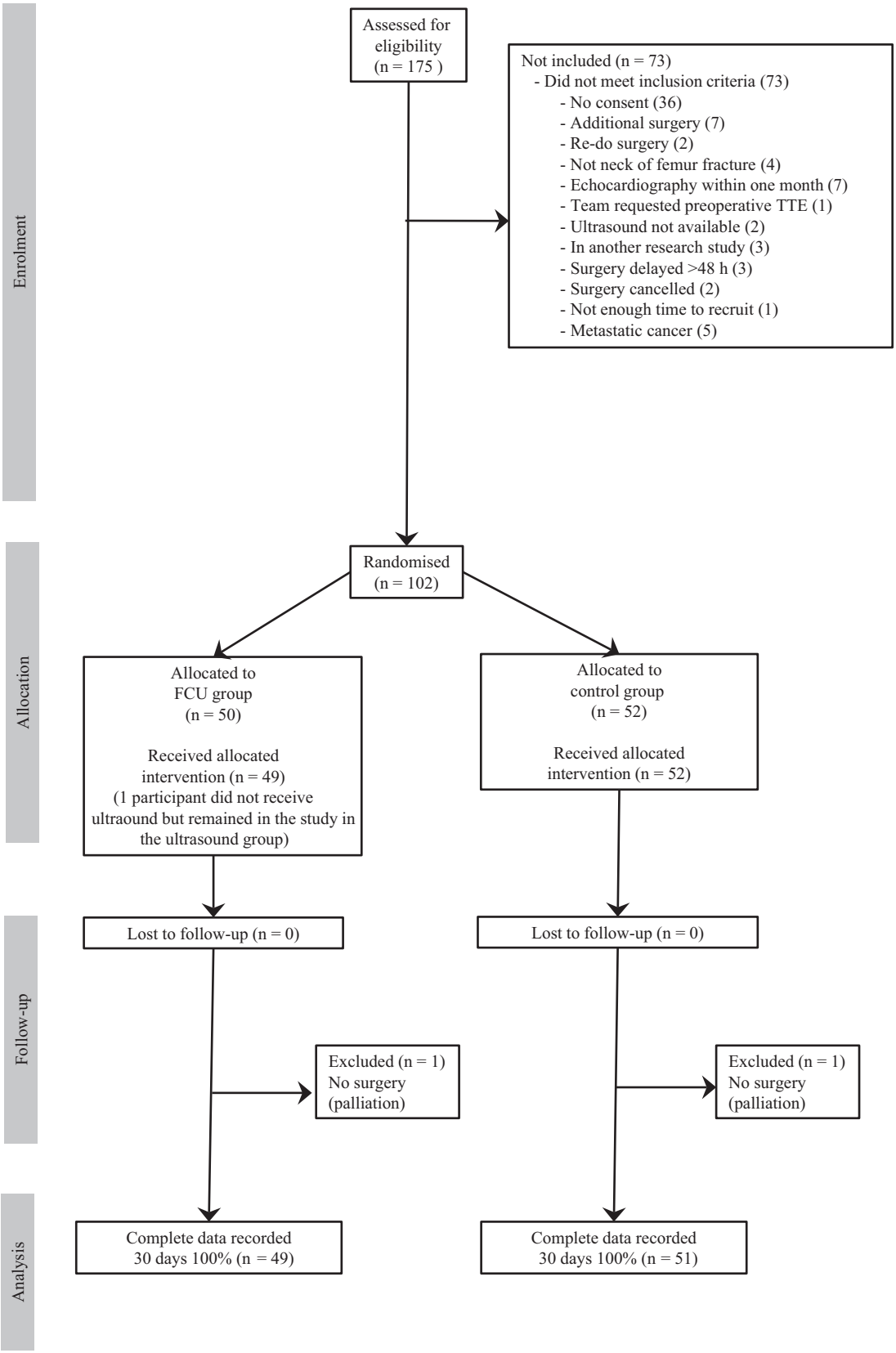

Figure 1 Participant flow chart. TTE, transthoracic echocardigography

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Table 2 Baseline characteristics, comorbidities, and procedural characteristics of 100 study participants. Values are number.

Variable	Total	Ultrasound group	Control group
Number of participants	100	49	51
Female	70	31	39
Hypertension	55	29	26
Cardiac failure	13	7	6
Ischaemic heart disease	16	9	7
Pulmonary hypertension	1	0	1
Valve disease	6	1	5
Cardiac dysrhythmia	35	18	17
Cerebrovascular disease	16	8	8
Chronic obstructive pulmonary disease	20	7	13
Diabetes mellitus	15	9	6
Renal impairment	3	1	2
High level of dependence	22	11	11
Surgery type			
Dynamic hip screw	39	21	18
Proximal femoral nail	28	13	15
Hemi-arthroplasty	26	10	16
Total hip replacement	7	5	2
Anaesthesia type			
General anaesthesia	85	48	37
Regional anaesthesia	15	1	14

deemed unfit for surgery by the treating team and palliative care ensued instead of surgery. These two participants were not deemed to be protocol violations. A participant flow chart is shown in Fig. 1.

Group baseline characteristics, comorbidities and procedural characteristics of the 100 study participants are shown in Table 2. The median (IQR [range]) age of the participants was 82 (74–88 [40–98]) years (ultrasound 82 (73–88 [47–98]) and control 83 (76–89 [40–98]) y). Pre-operative stay was 1 (1–1 [0–5]) days (ultrasound 1 (0–1 [0–3]) and control 1 (1–1 [0–5]) d). ASA status was 3 (3–4 [1–4]) (ultrasound 3 (3–4 [1–4]) and control 3 (3–4 [2–4])).

Pre-operative comorbidities recorded included: ASA physical status [26]; congestive cardiac failure [25]; ischaemic heart disease (either documented previous myocardial infarction, abnormal coronary angiogram or coronary revascularisation) [27]; valve disease of at least moderate severity [20, 21]; pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg or systolic pulmonary artery pressure > 35 mmHg [28]); dysrhythmia (documented atrial fibrillation, atrial flutter, ventricular tachycardia or ventricular fibrillation [25]); cerebrovascular disease (embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction [27]); chronic obstructive pulmonary disease (use of bronchodilators or steroids [29]); diabetes mellitus requiring oral hypoglycaemic or insulin therapy [29]; renal impairment (persistent elevated creatinine or requirement for intermittent peritoneal or haemodialysis [25]); and high level of dependence on full-time care.

Group primary and secondary outcomes are shown in Table 3. The median (IQR [range]) length of inpatient stay was 8 (6–12 [0–30]) days (ultrasound 7 (5–13 [3–30]) and control 9 (6–14 [0–30]) d). Intensive care length of stay was 1 (1–1 [0–1]) days (ultrasound 0 (1–1 [0–1]) and control 0 (0–0 [0–0]) d). The primary composite outcome at 30 days after surgery occurred in seven of the ultrasound group patients and 12 of the control group patients (relative group separation 39%).

Only the 30-day outcomes are reported, as the 90-day and 1-year outcome time-points have not passed for all participants to date.

Although there were no participants recorded to have suffered a non-fatal myocardial infarction or cardiac arrest, two out of the three participants in the ultrasound group that died may have been due to myocardial infarction, as the cause of death were recorded as myocardial infarction (pre-operative ultrasound revealed hypovolaemia) and cardiac failure (ultrasound revealed aortic stenosis with left and right ventricular failure). The cause of death in the third ultrasound patient was unknown (ultrasound revealed right ventricular failure, aortic and tricuspid regurgitation). The cause of death in the five participants in the control group participants was cerebrovascular accident, pulmonary embolism, surgical complications and two unknown.

Focused cardiac ultrasound findings in the 49 participants in the ultrasound group are shown in Table 4. Focused cardiac ultrasound led to a change in diagnosis in 26 and a change in management in 17 of the ultrasound-group participants; in nine cases, ultrasound identified significant unexpected pathology prompting stepped-up treatment, and in eight cases, ultrasound excluded significant suspected pathology, prompting stepped-down treatment (Table 5).

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Table 3 Group primary and secondary outcomes. Values are number.

	Total	Ultrasound group	Control group	Odds ratio	95%CI
Primary outcome					
Composite at 30 days	19	7	12	0.54	0.19–1.52
Secondary outcomes					
Mortality < 30 days	8	3	5	0.60	0.14–2.66
Morbidity < 30 days	11	4	7	0.56	0.15–2.04
Pulmonary embolus	4	2	2	1.04	0.14–7.71
Acute kidney injury (RIFLE 1)	6	1	5	0.19	0.02–1.70
Cardiac arrest	0	0	0	–	–
Cerebrovascular accident	1	1	0	–	–
Acute myocardial infarction	0	0	0	–	–
Congestive cardiac failure	8	0	8	–	–
New cardiac dysrhythmia	8	3	5	0.60	0.14–2.66
Respiratory failure	10	4	5	0.70	0.21–3.24
Pneumonia	15	4	11	0.32	0.10–1.10
Pulmonary aspiration	3	0	3	–	–
Pleural effusion(s)	8	2	6	0.32	0.06–1.67
Bronchospasm	1	0	1	–	–
Pneumothorax	0	0	0	–	–
Infection – uncertain origin	2	1	1	1.00	0.06–17.1
Infection – superficial surgical site	0	0	0	–	–
Infection – deep surgical site	0	0	0	–	–
Urinary tract infection	21	10	11	0.93	0.36–2.44

Discussion

This one-year pilot study comparing 30-day outcomes between hip fracture patients receiving or not receiving pre-operative focused cardiac ultrasound indicates that a larger, definitive study is feasible. The study achieved its aims, achieving a mean (SD) screening:recruitment ratio of 1.7 (0.2) and a mean recruitment rate of at least 2.2 patients.week^{-1} in the four participating hospitals, with only 1 out of 102 protocol violations, and group separation for the primary outcome of ≥ 20% (39%). Focused cardiac ultrasound did not appear to delay surgery and changed diagnosis and/or management in ≥ 25% (53% and 35%, respectively) of participants.

Based on a more conservative effect size of the primary outcome of 25% (39% in this pilot study) and control group incidence of primary outcome of 12 out of 51, using a two-tailed design, alpha of 0.05 and power of 0.9, a sample size of 984 participants per group will be required, which will be rounded up to 1000 participants in each group to account for attrition other than that caused by death. Using a conservative recruitment rate of one participant per site per week, to complete the trial in three years will require 13 sites.

Table 4 Focused cardiac ultrasound findings in 48 participants. Valve pathology indicates at least moderate stenosis or regurgitation according to recognised guidelines [20, 21]. Values are number.

	Number of participants
Normal	23
LV dysfunction	7
Systolic dysfunction	2
Diastolic dysfunction	3
Systolic + diastolic dysfunction	2
RV dysfunction	1
LV + RV dysfunction	1
Hypovolaemia	5
Vasodilation	1
Aortic stenosis	6
Isolated aortic stenosis	2
Aortic stenosis + ventricular dysfunction	4
Tricuspid regurgitation	4
Mitral regurgitation	1

LV, left ventricle; RV, right ventricle.

The primary outcome was designed to detect complications that could be primarily related to cardiac pathology, although other non-cardiac complications (such as pneumonia) could be indirectly influenced by

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Table 5 Stepped-up/down treatment changes after rediagnosis using focused cardiac ultrasound.

Clinical findings	Change in diagnosis from ultrasound	Change in management
Significant unexpected pathology diagnosed + treatment stepped-up		
Normal	Alerted to aortic stenosis, LV systolic and diastolic dysfunction, RV dysfunction, tricuspid regurgitation and PHT	Change from spinal anaesthesia to general anaesthesia. Insertion of arterial catheter and commencement of vasopressor infusion before anaesthesia.
Normal	Alerted to vasodilation	Change from spinal anaesthesia to general anaesthesia. Commencement of vasopressor infusion before anaesthesia
Normal	Alerted to aortic stenosis and LV diastolic dysfunction	Vasopressor and inotrope infusions
Normal	Alerted to hypovolaemia, mitral and tricuspid regurgitation	Fluids given before anaesthesia
Normal	Alerted to LV diastolic dysfunction, mitral and tricuspid regurgitation and PHT	Less fluids given than planned
Normal	Alerted to tricuspid regurgitation	Less fluids given than planned
AS, MR, LV + RV systolic dysfunction	Alerted to PHT, confirmed LV and RV systolic dysfunction, reassured no aortic stenosis or MR	Delay surgery for haemodialysis
LV+RV systolic+diastolic dysfunction	Alerted to aortic stenosis, confirmed LV and RV systolic and diastolic dysfunction	ICU postoperatively
LV systolic dysfunction	Alerted to right ventricular dysfunction, aortic and tricuspid regurgitation. Reassured no LV systolic dysfunction	Less fluids given
Significant pathology excluded, and treatment stepped down		
LV + RV systolic and diastolic dysfunction, aortic regurgitation	Reassured absence of RV failure and aortic regurgitation	No inotrope used
LV systolic dysfunction	Reassured absence of LV systolic dysfunction	More fluids given than planned
LV systolic dysfunction and hypovolaemia	Reassured absence of LV systolic dysfunction	More fluids given than planned
Pulmonary embolus and right ventricular dysfunction	Reassured absence of pulmonary embolus and right ventricular dysfunction. Alerted to LV diastolic dysfunction and pericardial effusion	More fluids given than planned
AS and regurgitation	Reassured absence of aortic regurgitation	More fluids given than planned
Hypovolaemia	Reassured absence of hypovolaemia	No fluids given before anaesthesia
Hypovolaemia and LV systolic dysfunction	Reassured absence of hypovolaemia and LV systolic dysfunction	Less fluids given than planned
AS and MR	Reassured absence of AS	No vasopressor infusion used

Valve pathology indicates at least moderate stenosis or regurgitation according to recognised guidelines [20, 21].
ICU, intensive care unit; LV, left ventricle; RV, right ventricle; PHT, pulmonary hypertension; AS, aortic stenosis; MR, mitral regurgitation.

cardiac disease, such as pulmonary venous congestion. Death was the most common contributor to the primary outcome, and group separation (point estimates) occurred in favour of the ultrasound group. Of note, the cardiac pathology identified on focused cardiac ultrasound in the three ultrasound participants who died was very severe, and death may have been unavoidable. One of the secondary aims of the proposed definitive trial will be to identify patterns of cardiac pathology where death is inevitable, prompting non-operative management. This may assist in end-of-life decisions including whether or not to proceed with surgery if it is deemed futile from the ultrasound findings.

Composite end-points consisting of binary events are frequently chosen as the primary outcome in medical trials of this nature and size, because no single outcome fully characterises the disease or outcome of interest and individual outcomes may occur rarely,

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therefore, the statistical power may be inadequate for any single outcome (e.g. death) [30]. This was found in our pilot study, where the prevalence of the composite outcome (19) was more than double that of mortality alone (8). For these reasons, chose a mortality and morbidity composite outcome based on the ENIGMA-2 trial [24], which involved patients at increased risk of cardiac disease undergoing non-cardiac surgery [24], representing a group with similar comorbid characteristics to the hip fracture population. We added mild acute kidney injury, as this occurs commonly and is associated with adverse outcomes after hip fracture surgery [31]. Non-fatal myocardial infarction and non-fatal cardiac arrest were not recorded in either group, although myocardial infarction was reported as the cause of death in two participants and cardiac failure in one participant. We accept that our pilot study may have missed episodes of non-fatal myocardial infarction, the detection of which we hope to improve in the proposed larger trial by using serial serum troponin and ECG measurement.

Given the considerable financial burden of in-patient care for hip fracture patients, we intend to investigate the cost implications of assessing patients using ultrasound compared with conventional assessment. Focused cardiac ultrasound incurs additional costs, related to capital purchase and maintenance, training, process time and care expansion (e.g. intensive care provision, additional surgery such as valve replacement), which may be balanced by financial savings consequent to complication rates, duration of inpatient stay and quality of life after hospital discharge.

This pilot study suggests that a larger, definitive randomised controlled trial is feasible; recruitment rates were achievable, protocol violations were rare and group separation of the primary, composite endpoint was achieved. Focused cardiac ultrasound did not appear to delay surgery and changed diagnosis and/or management in ≥ 25% (26 out of 49 and 17 out of 49, respectively) of participants. Based on a sample size of 2000 participants in 13 hospitals over three years, we estimate the definitive trial would cost an estimated AU$ 2.5 million (~£1.54 million, €1.67 million, US$ 2 million) to conduct.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Focused Cardiac Ultrasound report form.

Appendix S2. Definitions of primary and secondary outcomes of the proposed larger trial.

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